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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

MORAN, MARJORIE A

ART UNIT

PAPER NUMBER

1631

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/940,686

Applicant(s)

PALSSON ET AL.

Examiner

Marjorie A. Moran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 31 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 3,5,6 and 11-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4 and 7-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 8/27/01 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/12/02, 4/5/02, a.</u> | 6) <input type="checkbox"/> Other: _____ |

Election/Restrictions

Applicant's election of group I, claims 1-10 and species of metabolic network in prokaryotes in a paper filed 10/31/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3, 5-6, and 11-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in a paper filed 10/31/03.

An action on the merits of claims 1-2, 4, and 7-10, as they read on the elected species, follows.

Information Disclosure Statement

The IDS's filed 2/12/02, 4/5/02, and 8/18/03 have been considered in full.

Specification

The disclosure is objected to because of the following informalities: the first line of page 1 should indicate the --benefit of-- a priority application is claimed, not "priority to". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 4, and 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the optimal properties" in line 3 and "the desired optimal function" in line 7. There is insufficient antecedent basis for these limitations in the claim. The preamble recites achieving an optimal function, which does not provide antecedent basis for either term, therefore the claim is indefinite.

Claim 1, in step (a), recites calculating optimal properties of a "biochemical reaction network", but does not recite where the biochemical reaction network is to be found i.e. the cell of the preamble, some other cell, an entire organism, etc. As it is unclear what biochemical reaction network is to be "used" for the calculations of multiple steps in claim 1, claim 1 is indefinite.

Step (a) of claim 1 recites "using" optimization methods to calculate optimal properties of a biochemical reaction network. It is unclear what step or steps are intended by the term "using". It is further unclear what limitation(s) applicant intends by "optimization methods"; i.e. the metes and bounds intended by application for said methods are unclear. The examiner recommends rewriting the step with a positive, definite verb (e.g. calculating) and making clear what limitation is intended for "optimization methods".

Step (b) of claim 1 recites the term "recomputing" with regard to optimal properties. However, there is no initial step of "computing" anything in the claim,

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therefore it is unclear what applicant intends by "recomputing". It is noted that step (a) recites "using" methods to "calculate" optimal properties. This rejection may be overcome by rewriting step (a) to recite an active step of calculation (see above) and replacing the term "recomputing" in step (b) with --recalculating--.

Step (f) of claim 1 recites the term "evolve to" with respect to cultivated cells. The term "evolve" is generally defined in the art as "change over a (long) period of time". It is unclear if this is the definition intended by applicant for the term as it is used in the claim. No other definition is disclosed in the instant specification. As the cells have been constructed, it would seem that no further "evolution" or change is desired. Rather, the entirety of the claim and the disclosure of the specification indicate that the constructed (or engineered) cells are to be cultured to allow expression or detection of a desired optimal function. As it is unclear what meaning applicant intends for the phrase "evolve to" in the context of the claim, use of the phrase renders claim 1 indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4, and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over EDWARDS et al. (IDS ref: Biotech. Prog. (2000) vol. 16, pp. 927-939) in view of VARNER et al. (IDS ref: Curr. Opinion Biotech. (1999) vol. 10, pp. 146-150).

Claim 1 recites a method for achieving an optimal function of a biochemical reaction network in a cell by calculating optimal properties of a biochemical reaction network, altering a listing of reactions in the network and recalculating the optimal properties, repeating the alerting and recalculating until a desired optimal function is reached, constructing the genetic makeup of a cell to contain biochemical reactions which result in the calculated optimal function, and culturing the constructed cells to allow the optimal function to be expressed. Claim 2 limits the reaction network to be a

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metabolic network. Claim 4 limits the cells to be prokaryotic. Claim 7 limits the construction of a genetic makeup of a cell to be alteration of one or more genes of the cell. Claim 8 limits the gene alteration to be introduction of one or more genes. Claim 9 limits the gene alteration to be modification of an endogenous gene or genes. Claim 10 limits the biochemical reaction network to be a "substantially whole" (interpreted to be --complete--) reaction network.

EDWARDS teaches a method of determining optimal growth in *E. coli* using metabolic flux balance analysis (abstract and pp. 927-928). EDWARDS teaches that his method comprises changing reactions (and conditions) in a metabolic network, recalculating flux, and repeating such steps until an optimal flux is reached (p. 931 and Figure 4). EDWARDS teaches that his equations representing metabolic reactions comprise all feasible metabolic flux vectors (p. 929), which suggests that his equations represent "substantially all" metabolic reactions. EDWARDS teaches that growth of engineered cells may be determined in silico (e.g. p. 933 and Figure 5), and teaches that his models may be used to design metabolic networks in cells for industrial and further research purposes (p. 938). EDWARDS does not specifically teach culturing of engineered cells to allow expression of an optimal function, nor does EDWARDS specifically teach introduction or alteration of genes.

VARNER teaches that cybernetic (i.e. computer-implemented) models were used to predict actual growth/metabolism of genetically altered and cultured cells, including *E. coli* cells (p. 148). VARNER teaches that "genetic alteration" may include deletion and "gene-shuffling" (p. 148).

It would have been obvious to one of ordinary skill in the art at the time of invention to have cultured engineered cells, as taught by VARNER and suggested by EDWARDS, in order to allow development of a desired optimal function (growth) in the method of EDWARDS where the motivation is supplied by EDWARD's teaching to design cells for industrial use and further research. It would further have been obvious to have "engineered" the cells in the method of EDWARDS and VARNER using any form of genetic engineering, as suggested by VARNER's shuffling (modification of endogenous genes), and overexpression/deletion (suggesting addition/subtraction of genes), where the motivation is supplied by the teaching of both EDWARDS and VARNER that construction of engineered cells with optimal reaction networks is desired. One skilled in the art would reasonably have expected success in culturing genetically engineered cells in the method of EDWARDS and VARNER because VARNER teaches that cybernetic (in silico) modeling, such as that of EDWARDS, can be used to predict modification of enzyme expression and activity in the face of genetic ...perturbations (p. 148).

Conclusion

Claims 1-2, 4, and 7-10 are rejected; claims 3, 5-6, and 11-22 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (571) 272-0720. The examiner can normally be reached on Mon. to Wed, 7:30-4; Thurs 7:30-6; Fri 7-1 EST.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571)272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Marjorie A. Moran
Primary Examiner
Art Unit 1631

